MK- 0518

Drug Class: **Integrase Inhibitors**

Drug Description

MK-0518 is a leading candidate in a new class of antiretroviral medications called integrase inhibitors. Inhibition of integrase prevents insertion of HIV DNA into the human DNA genome, thus blocking the ability of HIV to replicate. [1]

HIV/AIDS-Related Uses

MK-0518 has been investigated in Phase II trials for the treatment of HIV in patients who are treatment-naive and in those who have multidrug-resistant infection. Phase III trials are underway to further investigate MK-0518 in patients who have multidrug-resistant infection.[2] [3]

On August 17, 2006, Merck opened a worldwide expanded access program (EAP) for HIV patients with limited or no treatment options. Enrollment into the EAP is scheduled to begin in the months following currently pending regulatory review and approvals. The EAP for MK-0518 is a noncomparative, multicenter, open-label, voluntary treatment use study. The study will continue until approximately 3 months after the drug is approved by the FDA and marketed. Enrolled patients will receive twice-daily 400 mg MK-0518, in addition to optimized background therapy; safety and tolerability will be monitored.[4]

Pharmacology

The integrase inhibitor MK-0518 is being investigated for the treatment of HIV infection in treatment-naive and in multi-drug-resistant patients in combination with approved antiretroviral therapies. MK-0518 is administered orally every twelve hours and does not require boosting with low-dose ritonavir to achieve therapeutic concentrations. MK-0518 is not a potent inhibitor or inducer of cytochrome P (CYP) 3A4, and it is predominantly metabolized by glucuronidation, specifically by the enzyme UDP-glucuronosyltransferase (UGT) 1A1.[5]

A two-part, Phase II, dose-ranging trial in treatment-naive patients compared 10-day MK-0518 monotherapy in 28 patients with placebo in seven patients. After 16 weeks of therapy, dosages of 100, 200, 400, or 600 mg twice-daily MK-0518 achieved greater than 50-fold viral load level reductions. Fifty to fifty-seven percent of patients taking MK-0518 achieved viral load levels less than 400 copies/ml, and 13% to 29% of patients achieved levels below 50 copies/ml.[6] In the second part of the study, 198 treatment-naive patients (including the initial 30 patients) were randomly assigned to receive either the same twice-daily dosages of MK-0518 or efavirenz 600 mg once daily, both in combination with tenofovir and lamivudine. After 24 weeks of therapy, 85% to 95% of patients on MK-0518-based regimens achieved viral loads of less than 50 copies/ml across all dosages. In the efavirenz-based regimen, 92% of patients achieved viral loads less than 50 copies/ml. However, viral load reduction was achieved more quickly with MK-0518 regimens.[7]

A second Phase II, randomized, double-blind, placebo-controlled trial compared 200, 400, and 600 mg twice-daily dosages of MK-0518 with placebo; all patients also received optimized background therapy (OBT). All patients were also failing highly active antiretroviral therapy (HAART) and had resistance to at least one drug in each anti-HIV drug class. At the 16-week interim analysis, the percentage of patients achieving viral load levels less than 400 copies/ml ranged from 64% to 84% across all doses studied, compared with 22% for placebo. The percentage of patients achieving viral load levels less than 50 copies/ml ranged from 56% to 72%, compared with 19% for placebo.[8]

In 2006, two Phase III, randomized, double-blind, placebo-controlled trials in patients failing HAART on OBT began and will evaluate the efficacy, safety, and tolerability of MK-0518, as compared to placebo.[9] [10]

Adverse Events/Toxicity

In Phase II studies, the most commonly reported treatment-related adverse effects were diarrhea, nausea, fatigue, headache, and itching. Other reported adverse effects included constipation,

Adverse Events/Toxicity (cont.)

flatulence, and sweating. Overall, MK-0518 was well tolerated, and its adverse effects were comparable to those in the placebo group.[11] [12] In the second part of one Phase II study, the most common adverse effects occurring after 24 weeks of treatment were headache, dizziness, and nausea. Eight serious nondrug-related adverse effects occurred overall (7/160 in the MK-0518 arm and 1/38 in the efavirenz arm); one patient taking twice-daily 600 mg MK-0518 discontinued treatment because of elevated liver function tests.[13]

Drug and Food Interactions

In completed trials, MK-0518 displayed no significant food effect.[14] MK-0518 appears compatible with all currently available antiretroviral medications.[15]

Clinical Trials

For information on clinical trials that involve MK-0518, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: MK-0518 AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[16]

Dosage Form: Dosages of 200, 400, and 600 mg MK-0518 taken every twelve hours have been studied for up to 16 weeks in Phase II trials.[17]

Other Names

MK0158[18]

Further Reading

Grinsztejn B, Nguyen BY, Katlama C, Gatell J, Lazzarin A, Vittecoq D, Gonzalez C, Chen J, Isaacs R, and the Protocol 005 Study Team. Potent Antiretroviral Effect of MK-0518, a Novel HIV-1 Integrase Inhibitor, in Patients with Triple-Class Resistant Virus. Denver, Abstract LB159, 2006.

James JS. Integrase inhibitors: first clear success in human trial. AIDS Treat News. 2005 Oct-Nov;(416):3-4. PMID: 16388543

A Study to Evaluate the Safety and Efficacy of MK-0518 in HIV-Infected Patients Failing Current Antiretroviral Therapies. Available at: http://clinicaltrials.gov/show/NCT00293267. Accessed 09/06/06.

A Study to Evaluate the Safety and Efficacy of MK-0518 in HIV-Infected Patients Failing Current Antiretroviral Therapies. Available at: http://clinicaltrials.gov/show/NCT00293254. Accessed 09/06/06.

Manufacturer Information

MK-0518
Merck & Company, Inc
One Merck Dr
P.O. Box 100
Whitehouse Station, NJ 08889-0100
(800) 609-4618

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

References

1. Merck & Company - Research and Development News: Merck Announces Interim Results from Phase II Study of MK-0518, an Investigational Oral HIV Integrase Inhibitor [press release], February 9, 2006. Available at: http://www.merck.com/newsroom/press_releases/research_and_development/2006_0209.html. Accessed 09/06/06.

2. Merck & Company - Research and Development News: Merck Announces Interim Results from Phase II Study of MK-0518, an Investigational Oral HIV Integrase Inhibitor [press release], February 9, 2006. Available at: http://www.merck.com/newsroom/press_releases/research_and_development/2006_0209.html. Accessed 09/06/06.

3. Natap.org - Conference Reports: 10th European AIDS Conference. MK-0518, the First Integrase Inhibitor for HIV, No Blarney. Available at: http://www.natap.org/2005/EACS/eacs_3.htm. Accessed 09/06/06.

4. Merck & Company - Corporate News: Expanded Access Program for MK-0518, an Investigational HIV Integrase Inhibitor, Established for Patients with Limited Available Treatment Options [press release], August 17, 2006. Available at: http://www.merck.com/newsroom/press_releases/corporate/2006_0817_print.html. Accessed 09/06/06.

5. Merck & Company - Research and Development News: Merck Announces Interim Results from Phase II Study of MK-0518, an Investigational Oral HIV Integrase Inhibitor [press release], February 9, 2006. Available at: http://www.merck.com/newsroom/press_releases/research_and_development/2006_0209.html. Accessed 09/06/06.

6. Natap.org - Conference Reports: 10th European AIDS Conference. MK-0518, the First Integrase Inhibitor for HIV, No Blarney. Available at: http://www.natap.org/2005/EACS/eacs_3.htm. Accessed 09/06/06.

7. Merck & Company - Research and Development News: An Investigational Oral HIV Integrase Inhibitor, MK-0518, in Combination Therapy Achieved Comparable HIV RNA Reduction to Efavirenz in Combination Therapy in Treatment-Naive, HIV Infected Patients at 24 Weeks [press release], August 12, 2006. Available at: http://www.merck.com/newsroom/press_releases/research_and_development/2006_0812.html. Accessed 09/06/06.

8. Merck & Company - Research and Development News: Merck Announces Interim Results from Phase II Study of MK-0518, an Investigational Oral HIV Integrase Inhibitor [press release], February 9, 2006. Available at: http://www.merck.com/newsroom/press_releases/research_and_development/2006_0209.html. Accessed 09/06/06.

9. ClinicalTrials.gov - A Study to Evaluate the Safety and Efficacy of MK-0518 in HIV-Infected Patients Failing Current Antiretroviral Therapies. Available at: http://clinicaltrials.gov/show/NCT00293267. Accessed 09/06/06.

10. ClinicalTrials.gov - A Study to Evaluate the Safety and Efficacy of MK-0518 in HIV-Infected Patients Failing Current Antiretroviral Therapies. Available at: http://clinicaltrials.gov/show/NCT00293254. Accessed 09/06/06.

11. Merck & Company - Research and Development News: Merck Announces Interim Results from Phase II Study of MK-0518, an Investigational Oral HIV Integrase Inhibitor [press release], February 9, 2006. Available at: http://www.merck.com/newsroom/press_releases/research_and_development/2006_0209.html. Accessed 09/06/06.

12. Natap.org - Conference Reports: 10th European AIDS Conference. MK-0518, the First Integrase Inhibitor for HIV, No Blarney. Available at: http://www.natap.org/2005/EACS/eacs_3.htm. Accessed 09/06/06.

13. Merck & Company - Research and Development News: An Investigational Oral HIV Integrase Inhibitor, MK-0518, in Combination Therapy Achieved Comparable HIV RNA Reduction to Efavirenz in Combination Therapy in Treatment-Naive, HIV Infected Patients at 24 Weeks [press release], August 12, 2006. Available at: http://www.merck.com/newsroom/press_releases/research_and_development/2006_0812.html. Accessed 09/06/06.

14. Natap.org - Conference Reports: 10th European AIDS Conference. MK-0518, the First Integrase Inhibitor for HIV, No Blarney. Available at: http://www.natap.org/2005/EACS/eacs_3.htm. Accessed 09/06/06.

15. Merck & Company - Research and Development News: Merck Announces Interim Results from Phase II Study of MK-0518, an Investigational Oral HIV Integrase Inhibitor [press release], February 9, 2006. Available at: http://www.merck.com/newsroom/press_releases/research_and_development/2006_0209.html. Accessed 09/06/06.

16. Merck & Company - Research and Development News: Merck Announces Interim Results from Phase II Study of MK-0518, an Investigational Oral HIV Integrase Inhibitor [press release], February 9, 2006. Available at: http://www.merck.com/newsroom/press_releases/research_and_development/2006_0209.html. Accessed 09/06/06.

17. Merck & Company - Research and Development News: Merck Announces Interim Results from Phase II Study of MK-0518, an Investigational Oral HIV Integrase Inhibitor [press release], February 9, 2006. Available at: http://www.merck.com/newsroom/press_releases/research_and_development/2006_0209.html. Accessed 09/06/06.

18. MeSH - Available at: http://nlm.nih.gov/mesh/cgi/MBrowser.html. Accessed 09/06/06.